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(54) FLAVONOID PHOSPHATES OF AMINOGLYCOSIDE ANTIBIOTICS
(71) MERCK PATENT GESELLSCHAFT MIT BESCHRANKTER HAFTUNG
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(72) DR. HELMUT WAHLIG, DR. ELVIRA DINGELDEIN, DR. RICHARD
KIRCHLECHNER, DR. DIETER ORTH AND DR. WERNER ROGALSKI
(74) CA
(57) Claim

3. Gentamycin hesperidin-phosphate.
- 4.a) Neomycin hesperidin-phosphate.
- b) Paromomycin hesperidin-phosphate.
- c) Sisomycin hesperidin-phosphate.
- d) Amikacin hesperidin-phosphate.
- e) Tobramycin hesperidin-phosphate.
- f) Dibekacin hesperidin-phosphate.
- g) Streptomycin hesperidin-phosphate.

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COMPLETE SPECIFICATION

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Name of Applicant: MERCK PATENT GESELLSCHAFT MIT
BESCHRANKTER HAFTUNG

Address of Applicant: Frankfurter Strasse 250, D-6100 Darmstadt,
Germany

Actual Inventor: 1) Dr. Helmut Wahlig 4) Dr. Dieter Orth
2) Dr. Elvira Dingeldein 5) Dr. Werner Rogalski
3) Dr. Richard Kirchlechner

Address for Service: ARTHUR S. CAVE & CO., Patent and Trade Mark
Attorneys, 1 Alfred Street, Sydney, New
South Wales, Australia, 2000.

Complete Specification for the invention entitled: "SPARINGLY SOLUBLE
SALTS OF AMINOGLYCOSIDE ANTIBIOTICS"

The following statement is a full description of this invention,
including the best method of performing it known to ~~me~~ us:-

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Sparingly soluble salts of aminoglycoside antibiotics

The invention relates to new sparingly soluble salts of aminoglycoside antibiotics.

Aminoglycoside antibiotics such as gentamycin or
5 tobramycin are usually employed in the form of their sul-
fates, which are readily soluble in water. The anti-
biotics are rapidly released from these salts and distri-
bute themselves around the body. In some cases, this
property is a disadvantage, in particular if an infection
10 which is limited locally is to be combated, for example
an infected bone. In these cases, more sparingly
soluble salts, from which the antibiotic is released more
slowly and which therefore can display a certain depot
action, are desirable.

15 Some sparingly soluble salts of aminoglycoside
antibiotics are known. Thus, for example, U.S. Patent
Specification 3,091,572 mentions various sparingly soluble
salts of gentamycin (for example salts with fatty acids
which contain 8 or more C atoms, such as lauric acid,
20 stearic acid, palmitic acid or oleic acid, aralkanoic
acids, such as phenylbutyric acid, arylcarboxylic acids,
such as naphthalene-1-carboxylic acid, and sulfuric and
sulfonic acids, such as laurylsulfuric acid and dodecyl-
benzenesulfonic acid).

25 It has been found that these salts display certain
disadvantages when used. Thus, they have a waxy,
clearly hydrophobic nature which impedes their galenical
processing.

The invention was based on the object of discover-

ing new salts of antibiotics which are sparingly soluble and which do not have the adverse properties of the known antibiotic salts or display them to only a minor degree. This object was achieved by providing the new salts.

5 It has been found that a slower release of the antibiotics can be achieved if the sparingly soluble flavonoid phosphates, in particular the hesperidin-phosphates, of the aminoglycoside antibiotics are used instead of the sulfates mentioned or other readily soluble salts.

10 The invention accordingly relates to the flavonoid phosphates, in particular the hesperidin-phosphates, of aminoglycoside antibiotics.

Suitable anionic components of the salts according to the invention are phosphoric acid half-esters of
15 hydroxyflavonoids, for example of hydroxy-flavanes, -flavenes, -flavanones, -flavones or -flavylium salts. The flavanone and flavone derivatives are preferred.

The hydroxyflavonoids can contain one or more, for example 1, 2, 3, 4, 5, 6 or 7, preferably 1, 2, 3 or 4,
20 hydroxyl groups, which are preferably of a phenolic nature, but can also be of the alcoholic type. They are as a rule in the 3-, 5-, 6-, 7-, 3'- and/or 4'-position of the flavane system, but can also be in the 4-, 8-, 2'-, 5'- or 6'-position. The 3'- and 5'-positions
25 are preferred. One or more of the hydroxyl groups can be esterified with phosphoric acid. Thus, for example, the 3'- and 5'-monophosphates and the 3',5 -diphosphate of hesperidin can be used as salt-forming components.

In the following text, the expression "hesperidin-phosphoric

acid" relates to the 3',5-diphosphate and the expression "hesperidin-phosphates" relates to the salts derived therefrom.

In addition to the phosphorylated and free OH groups, the flavonoid phosphoric acids can also carry other substituents, for example etherified OH groups, such as alkoxy groups with, preferably, 1 - 4 C atoms, above all methoxy groups (as a rule not more than three, preferably one, and preferably in the 4'-position, but also in the 3-, 3'-, 5-, 6- and/or 7-position), and, in particular, glycosidated OH groups. These can be glycosidated with mono-, di-, tri- or tetra-saccharides. Preferred glycoside components are monosaccharides such as D-glucose, and also D-galactose, D-glucuronic acid, D-galacturonic acid, D-xylose, D-apiose, L-rhamnose and L-arabinose, and disaccharides such as rhamnosylglucoses, particularly preferably rutinose and neohesperidose, and also, for example, runggiose, robinobiose, sophorose, gentiobiose, apiobiose, vicianose, sambubiose, primverose or latyrose. Glycosidated OH groups are preferably in the 7- and/or 3-position; at most 2, and preferably one, glycosidated OH groups are as a rule present in the molecule of the flavonoid phosphoric acid. Examples of other possible substituents (as a rule not more than 3, preferably only one) are alkyl with, for example, 1 - 4 C atoms, preferably methyl, halogen, preferably F or Cl, and hydroxyalkoxy with, for example, 1 - 4 C atoms, preferably 2-hydroxyethoxy.

Examples of specific flavonoid phosphates are

phosphoric acid half-esters of hydroxyflavanes, such as 6-hydroxy-4'-methoxyflavane, 6-hydroxy-3,4'-dimethoxyflavane, 6-hydroxy-4'-methoxy-3-methylflavane, catechol ((+)-3,3',4',5,7-pentahydroxyflavane) and leucocianidol (3,3',4,4',5,7-hexahydroxyflavane) and glycosides thereof, such as 2,3,3',4,4',5,7-heptahydroxyflavane glucoside; hydroxyflavanones, such as liquiritigenin (4',7-dihydroxyflavanone), pinocembrin (dihydrochrysin, 5,7-dihydroxyflavanone), naringenin (4',5,7-trihydroxyflavanone), eriodictyol (3',4',5,7-tetrahydroxyflavanone), dihydroquercetin (taxifolin, 3,3',4',5,7-pentahydroxyflavanone), 6-hydroxy-4'-methoxyflavanone, sacuranetin (4',5-dihydroxy-7-methoxyflavanone), isosacuranetin (5,7-dihydroxy-4'-methoxyflavanone), hesperetin (3',5,7-trihydroxy-4'-methoxyflavanone) and silibinin (2-[trans-2-(4-hydroxy-3-methoxyphenyl)-3-hydroxymethyl-1,4-benzodioxan-6-yl]-3,5,7-trihydroxychroman-4-one) and glycosides thereof, such as pinocembrin 7-rutinoside, sarothanoside (pinocembrin 7-neohesperidoside), salipurposide (naringenin 5-glucoside), prunin (naringenin 7-glucoside), narirutin (naringenin 7-rutinoside), naringin (naringenin 7-neohesperidoside), eriodictin (eriodictyol 7-rhamnoside), erio-citrin (eriodictyol 7-rutinoside), eriodictyol 7-neohesperidoside, didymin (isosacuranetin 7-rutinoside), poncirin (isosacuranetin 7-neohesperidoside), persicoside (hesperitin glucoside), hesperidin (hesperetin 7-rutinoside), and neohesperidin (hesperetin 7-neohesperidoside); hydroxyflavones, such as chrysin (5,7-dihydroxyflavone), primetin (5,8-dihydroxyflavone), galangin (3,5,7-tri-

hydroxyflavone), baicalein (5,6,7-trihydroxyflavone), apigenin (4',5,7-trihydroxyflavone), datiscetin (2',3,5,7-tetrahydroxyflavone), lotoflavin (2',4',5,7-tetrahydroxyflavone), caempferol (3,4',5,7-tetrahydroxyflavone), fisetin (3,3',4',7-tetrahydroxyflavone), luteolin (3',4',5,7-tetrahydroxyflavone), scutellarein (4',5,6,7-tetrahydroxyflavone), morin (2',4,4',5,7-pentahydroxyflavone), robinetin (3,3',4',5',7-pentahydroxyflavone), quercetin (3,3',4',5,7-pentahydroxyflavone), tectochrysin (5-hydroxy-7-methoxyflavone), genkwanin (4',5-dihydroxy-7-methoxyflavone), acacetin (5,7-dihydroxy-4'-methoxyflavone), diosmetin (3',5,7-trihydroxy-4'-methoxyflavone), chrysoeriol (4',5,7-trihydroxy-3'-methoxyflavone), rhamnetin (3,3',4',5-tetrahydroxy-7-methoxyflavone), isorhamnetin (3,4',5,7-tetrahydroxy-3'-methoxyflavone), chloroflavinonin (3'-chloro-2',5-dihydroxy-3,7,8-trimethoxyflavone) and eupatorin (3',5-dihydroxy-4',6,7-trimethoxyflavone) and glycosides thereof, such as chrysin 7-rutinoside, chrysin 7-neohesperidoside, apiin (apigenin 7-apiosylglucoside), rhoifolin (apigenin 7-neohesperidoside), isorhoifolin (apigenin 7-rutinoside), nicotiflorin (caempferol 3-rutinoside), lespedin (caempferol 3,7-dirhamnoside), robinin (caempferol 3-robinoside 7-rhamnoside), scolymoside (lonicerin, luteolin 7-rutinoside), veronicastroside (luteolin 7-neohesperidoside), quercitrin (quercetin 3-rhamnoside), isoquercitrin (quercetin 3-glucoside), hyperoside (quercetin 3-galactoside), rutoside (rutin, quercetin 3-rutinoside), 6-hydroxymethylrutoside, monoxerutin [7-(2-hydroxyethyl)-rutoside], ethoxazorutoside [4'-O-(2-morpho-

linoethyl)-rutoside], troxerutin [3',4',7-tris-(2-hydroxyethyl)-rutoside], acaciin (linarin, acacetin 7-rutinoside), fortunellin (acacetin 7-neohesperidoside), diosmin (diosmetin 7-rutinoside), neodiosmin (diosmetin 7-neohesperidoside) and narcissin (isorhamnetin 3-rutinoside); hydroxyflavylium salts, such as cyanidin and glycosides thereof, such as keracyanin (cyanidin 3-rutinoside).

Possible aminoglycoside antibiotics are, in particular, those which contain a deoxystreptamine unit.

Specific examples which are particularly preferred are amikacin, dibekacin, gentamycin, the neomycins, paromomycin, sagamycin, sisomicin, streptomycin and tobramycin, and further preferred examples are allomycin, amicitin, apramycin, bekanamycin, betamicin, butirosin, destomycin, the everninomycins, the ezomycins, flambamycin, fortimycin A and B, framycetin, hikizimycin, homomycin, hybrimycin, hygromycin, the kanamycins, kasugamycin, lividomycin, minosaminomycin, the myomycins, netilmicin, parvulomycin, puromycin A, ribostamycin, rimocidin, ristomycin, ristamine, the seldomycins, sorbistin, spectinomycin, streptothricin, tunicamycin and verdamycin and epimers and derivatives thereof which are basic.

Since some of these antibiotics, for example gentamycin, are known not to be single substances but mixtures (gentamycin is, for example, a mixture of the compounds gentamycin C 1, gentamycin C 2 and gentamycin C 1a), the flavonoid phosphates in some cases are also not single substances but mixtures. Moreover, since many of the antibiotics mentioned, for example all the gentamycins,

contain several basic nitrogen atoms, and since, on the other hand, flavonoid phosphoric acids such as hesperidin-phosphoric acid are polybasic acids, it is furthermore possible for acid, neutral and/or basic salts to be
5 formed. All these possible salts and their mixtures with one another are included in the definition "flavonoid phosphates of aminoglycoside antibiotics".

The neutral salts and mixtures containing these are preferred; in the case of the gentamycin hesperidin-
10 phosphates, for example, the salt (mixture) of 2 mols of gentamycin and 5 mols of hesperidin-phosphoric acid is particularly preferred. ("Neutral" in this context means that there is one basic amino group per phosphoric acid radical).

15 The invention also relates to a process for the preparation of flavonoid phosphates of aminoglycoside antibiotics, characterised in that a water-soluble salt of an aminoglycoside antibiotic is reacted with a flavonoid phosphate or one of its water-soluble salts.

20 The preparation is carried out in a manner which is known per se, for example by bringing together an aqueous solution of the water-soluble salt of the antibiotic (for example gentamycin sulfate) and an aqueous solution of the flavonoid phosphate or one of its water-
25 soluble salts (for example the disodium salt), preferably whilst stirring and at room temperature. An organic solvent, for example an alcohol, such as ethanol, may also be added to improve the solubility. The flavonoid phosphates formed are sparingly soluble in water and can

be obtained by filtering, washing with water, and drying.

The invention furthermore relates to the use of the flavonoid phosphates mentioned for the preparation of pharmaceutical formulations, in particular by a non-
5 chemical route. For this, they can be brought into a suitable dosage form together with at least one solid, liquid or semi-liquid excipient or auxiliary, if appropriate in combination with one or more other active compound(s).

10 The invention furthermore relates to agents, in particular pharmaceutical formulations, containing at least one flavonoid phosphate of an aminoglycoside antibiotic.

These formulations can be used as medicaments in
15 human or veterinary medicine. Possible excipients are organic or inorganic substances which are suitable for enteral (for example oral) or parenteral administration or topical application and which do not react with the new compounds, for example water, vegetable oils, benzyl alcohols, polyethylene glycols, glycerol triacetate, gelatin,
20 carbohydrates, such as lactose or starch, magnesium stearate, talc or petroleum jelly. Tablets, dragées, capsules, syrups, elixirs or drops are used, in particular, for oral administration, suppositories are used for
25 rectal administration, solutions, suspensions, emulsions or implants are used for parenteral administration, and ointments, creams or powders are used for topical application. Implants, f.e. based on silicone rubber, tricalcium phosphate or collagen, which are suitable, for example, for
30 the treatment of infected bone, are of particular import-

ance. The new compounds can also be lyophilised and the resulting lyophilisates can be used, for example, for the preparation of injection products. The formulations mentioned can be sterilised and/or can contain auxiliaries, such as lubricants, preservatives, stabilisers and/or wetting agents, emulsifiers, salts for influencing the osmotic pressure, buffer substances, colorants, flavour substances and/or aroma substances. If desired, they can also contain one or more other active compounds, for example readily soluble salts of the same or different antibiotics, in order to achieve a systemic action in addition to the depot effect caused by the flavonoid phosphates.

The invention particularly relates to a new fibrin/antibiotic gel which contains at least one flavonoid phosphate of an aminoglycoside antibiotic.

Fibrin/antibiotic gels which contain tobramycin, gentamycin and/or one of their physiologically acceptable salts as the antibiotic are known from International Patent Application WO 81/00516. In that application, only the sulfates are mentioned specifically as physiologically acceptable salts of the two antibiotics. However, these known fibrin/antibiotic gels which contain tobramycin sulfate or gentamycin sulfate have the disadvantage when used in practice, for example in the treatment of infected bone, that the antibiotics are released from them too rapidly. The antibiotics distribute themselves about the body and are partly excreted; they can then no longer be effective to the desired extent at the actual infection site. The new fibrin/antibiotic gel

does not have these adverse properties of the known gels, or has them only to a minor degree.

The gentamycin salts can be used in the form in which they are obtained or in finely divided, for example, 5 micronised, form for the preparation of the fibrin/antibiotic gels.

The fibrin/antibiotic gels can be prepared in a manner which is known per se, preferably by mixing a fibrinogen solution, a thrombin solution and the new 10 flavonoid phosphate of an aminoglycoside antibiotic. The fibrin is thereby precipitated. The thrombin solution preferably additionally contains aprotinin and/or is enriched with calcium ions, for example in the form of CaCl_2 . 15 Apart from the flavonoid phosphates, all the constituents of the gel are advantageously used in the form of conventional commercially available products. It is possible to form the gel first at the chosen location, for example directly in the bone cavity, by addition of the thrombin solution to the fibrinogen solution, the salt of 20 the antibiotic being added beforehand either to the thrombin solution or to the fibrinogen solution. However, the gel is preferably prepared by mixing the constituents outside the body. In both cases, the coagulation operation of the fibrin can be controlled with respect to 25 time by changing the concentration of the thrombin.

The fibrinogen can be used, for example, in the form of human fibrinogen as a commercially available cryoprecipitate which contains about 90 mg/ml of protein which, can be precipitated with thrombin, or in the form of a

lyophilisate, for example obtained from human blood from pooled donor plasma. The fibrin/antibiotic gel preferably contains about 2 to about 10, preferably about 3 to 6, per cent by weight of fibrin.

5 The thrombin solution is preferably prepared by dissolving thrombin (for example in the form of a powder) in an aqueous calcium chloride solution. This can contain, for example, 1,000 to 10,000 KIU (kallikrein inactivator units), preferably about 3,000 KIU, of aprotinin per
10 ml. The concentration of calcium chloride is preferably about 20 to 60, in particular about 40, mmols/l. The concentration of the thrombin is preferably between about 10 and about 500 NIH units per ml. About the same volumes of fibrinogen solution and thrombin solution
15 are preferably used for preparing the gel.

The salt of the antibiotic is advantageously used in an amount based on the body weight, and the maximum daily dose should be taken into consideration. The concentration of the antibiotic in the fibrin/antibiotic
20 gel is preferably between about 0.5 and about 10, in particular between 1 and 5, per cent by weight, relative to the base of the aminoglycoside antibiotic.

The coagulation time of the gel depends on the thrombin concentration. The plastic formability of the
25 resulting coagulant can be maintained for a period of $\frac{1}{2}$ to 1 minute if a thrombin concentration of about 150 NIH units per ml is used. The flow properties of the gel are maintained for a considerably longer period (for example up to 3 minutes) by a lower thrombin concentration

(10 - 15 NIH units/ml). The coagulation of the fibrin is thereby slowed down, and the tensile strength of the polymer is rather increased.

As well as the salts which can be used according to the invention, the gels can additionally also contain other physiologically acceptable gentamycin salts, for example the sulfate or gentamycin base, as well as other antibiotics, such as tobramycin, neomycin, streptomycin, penicillins, bacitracin, clindamycin and/or physiologically acceptable salts thereof. The gels can also contain other active compounds.

In case of primary spongiosa graft, the fibrin/antibiotic gel not only controls infection but also improves the osteogenetic potency of the biological implant.

Bone which is in danger of infection, for example following fractures, can, of course, also be treated with the fibrin/antibiotic gel to prevent infection. In this case, a particularly high local level of active compound is achieved by the special gentamycin salts.

The delayed release of the antibiotic from the fibrin/antibiotic gels according to the invention in comparison with the release from gels obtained with gentamycin sulfate can be demonstrated in a manner which is known per se, the gentamycin released preferably being determined microbiologically. This determination can be effected in vitro, for example by elution in aqueous buffer solution or animal or human serum. The rate of excretion in the urine or the change of the concentration in the

serum or in tissues with respect to time can also be determined in the same way following implantation of the gel in vivo or following a bone operation. In vivo experiments can be carried out on any desired experimental
5 animals, for example rats, rabbits or dogs, or on humans.

The invention also relates to the use of the flavonoid phosphates mentioned in combating illnesses, in particular bacterial infections, and to their use in the therapeutic treatment of the human or animal body.

10 The substances according to the invention are preferably administered for these purposes in dosages of between about 5 and 1,000 mg, in particular between 10 and 500 mg, per dosage unit (relative to the antibiotic active compound). The particular dose for each parti-
15 cular patient depends, however, on the most diverse factors, for example on the effectiveness of the particular compound employed, and the age, weight, general state of health and sex, on the diet, on the time and route of administration, and on the excretion rate, medicament com-
20 bination and severity of the particular illness to which the therapy applies. Local administration is preferred.

In the examples which follow, the temperatures are given in °C.

Example 1

25 A solution of 20.4 g (25 mmols) of disodium hesperidin-5,3'-diphosphate in 600 ml of water is added to a solution of 7.07 g (10 mmols) of gentamycin sulfate in 200 ml of water at 20°, whilst stirring.

Stirring is continued for one hour, the resulting

gentamycin hesperidin-phosphate (gentamycin . 2.5 hesperidin-phosphate) is filtered off with suction, rinsed with water and dried over KOH. M.p. 227 - 229° (decomposition); IR spectrum (in KBr): 3410, 2950, 1637, 1572, 1510 and 1440 cm^{-1} .

Examples 2 to 8

The following compounds are obtained from the calculated amounts of the sulfates of the corresponding antibiotics and disodium hesperidin-5,3'-diphosphate analogously to Example 1:

2. Neomycin hesperidin-phosphate (= neomycin . 3 hesperidin-phosphate), m.p. 228 - 230° (decomposition).
3. Paromomycin hesperidin-phosphate (= paromomycin . 2.5 hesperidin-phosphate), m.p. 219 - 222° (decomposition).
4. Sisomycin hesperidin-phosphate (= sisomycin . 2.5 hesperidin-phosphate), m.p. 220 - 221° (decomposition).
5. Amikacin hesperidin-phosphate (= amikacin . 2 hesperidin-phosphate), m.p. 226 - 229° (decomposition).
6. Tobramycin hesperidin-phosphate (= tobramycin . 2.5 hesperidin-phosphate), m.p. 228° (decomposition).
7. Dibekacin hesperidin-phosphate (= dibekacin . 2.5 hesperidin-phosphate), m.p. 230° (decomposition).
8. Streptomycin hesperidin-phosphate (= streptomycin . 3 hesperidin-phosphate), m.p. 212 - 213° (decomposition).

Example 9

A solution of 7.07 g of gentamycin sulfate in 200 ml of water is added to a solution of 17.5 g (50 mmols) of 6-hydroxy-4'-methoxy-flavanone-6-phosphoric acid ester in 150 ml of ethanol and 1,600 ml of water at 20°, whilst

stirring. Stirring is continued for one hour and the resulting gentamycin salt of 6-hydroxy-4'-methoxy-flavanone-6-phosphoric acid ester is filtered off with suction, rinsed with water and dried over KOH. M.p. 210 - 215°
5 (sintering at 190°).

The examples which follow relate to pharmaceutical formulations which contain hesperidin-phosphates of aminoglycoside antibiotics:

Example A: Capsules

10 10 kg of neomycin hesperidin-phosphate are introduced into hard gelatin capsules in the usual way, so that each capsule contains active compound corresponding to 165 mg of neomycin base.

Example B: Ampoules

15 1 kg of gentamycin hesperidin-phosphate is finely micronised and suspended in 30 l of sesame oil and the suspension is introduced into ampoules, which are sealed under sterile conditions. Each ampoule contains active compound corresponding to 10 (40, 80, 120) mg of gentamycin base.
20

Example C: Implants

1.54 g of micronised gentamycin hesperidin-phosphate (corresponding to 0.2 g of gentamycin) are mixed with 8.5 g of silicone rubber monomer (Medical Grade
25 Silastic 382, Dow Corning), 2 drops of polymerisation catalyst are added, the components are mixed again and the mixture is shaped into circular discs 20 mm in diameter and 1 mm thick. Each disc contains 6 mg of gentamycin base.

Example D:

Fibrin/antibiotic gel

4 NIH units of thrombin (commercial product) are dissolved in 1 ml of aprotinin/calcium chloride solution (commercial product; 3,000 KIU/ml of aprotinin in 40 mmols/l of CaCl_2), the solution is warmed to 37°, an amount of gentamycin hesperidin-phosphate corresponding to 20 mg of gentamycin base is added and the mixture is mixed with the same amount of "fibrin adhesive" (commercial product; prepared by low-temperature precipitation from human donor plasma; stored at -18° or below; 1 ml of the solution contains on average 90 mg of protein which can be precipitated with thrombin, total protein content of the solution about 10 per cent by weight; thawed for about 20 - 30 minutes before the planned use), which has been prewarmed to 37°. The mixture is allowed to solidify in stainless steel cylinders (internal diameter 6 mm, height 10 mm) (1 ml for 3 cylinders). The gel cylinders formed are then ejected from the moulds.

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D a r m s t a d t

The claims defining the invention are as follows:

1. Flavonoid phosphates of aminoglycoside antibiotics.
2. Hesperidin-phosphates of aminoglycoside antibiotics.
3. Gentamycin hesperidin-phosphate.
- 4.a) Neomycin hesperidin-phosphate.
b) Paromomycin hesperidin-phosphate.
c) Sisomycin hesperidin-phosphate.
d) Amikacin hesperidin-phosphate.
e) Tobramycin hesperidin-phosphate.
f) Dibekacin hesperidin-phosphate.
g) Streptomycin hesperidin-phosphate.
5. Process for the preparation of flavonoid phosphates of aminoglycoside antibiotics, characterised in that a water-soluble salt of an aminoglycoside antibiotic is reacted with a flavonoid phosphate or one of its water-soluble salts.
6. Process for the preparation of pharmaceutical formulations, characterised in that a flavonoid phosphate of an aminoglycoside antibiotic is brought into a suitable dosage form together with at least one solid, liquid or semi-liquid excipient or auxiliary, if appropriate in combination with one or more other active compound(s).
7. Pharmaceutical formulation, characterised in that it contains at least one flavonoid phosphate of an aminoglycoside antibiotic.

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8. Fibrin antibiotic gel containing at least one flavonoid phosphate of an aminoglycoside antibiotic.
9. A method of combatting illnesses in animals comprising the use of flavonoid phosphates of aminoglycoside antibiotics.
10. Flavonoid phosphates of aminoglycoside antibiotics when used in combatting illnesses in animals.
11. Flavonoid phosphates as herein described.

~~DATED this 9th day of June, 1986~~

MERCK PATENT GESELLSCHAFT
MIT BESCHRANKTER HAFTUNG

BY Its Patent Attorneys

ARTHUR S. CAVE & CO.



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